Agony and Irony

The Opium War: Why?

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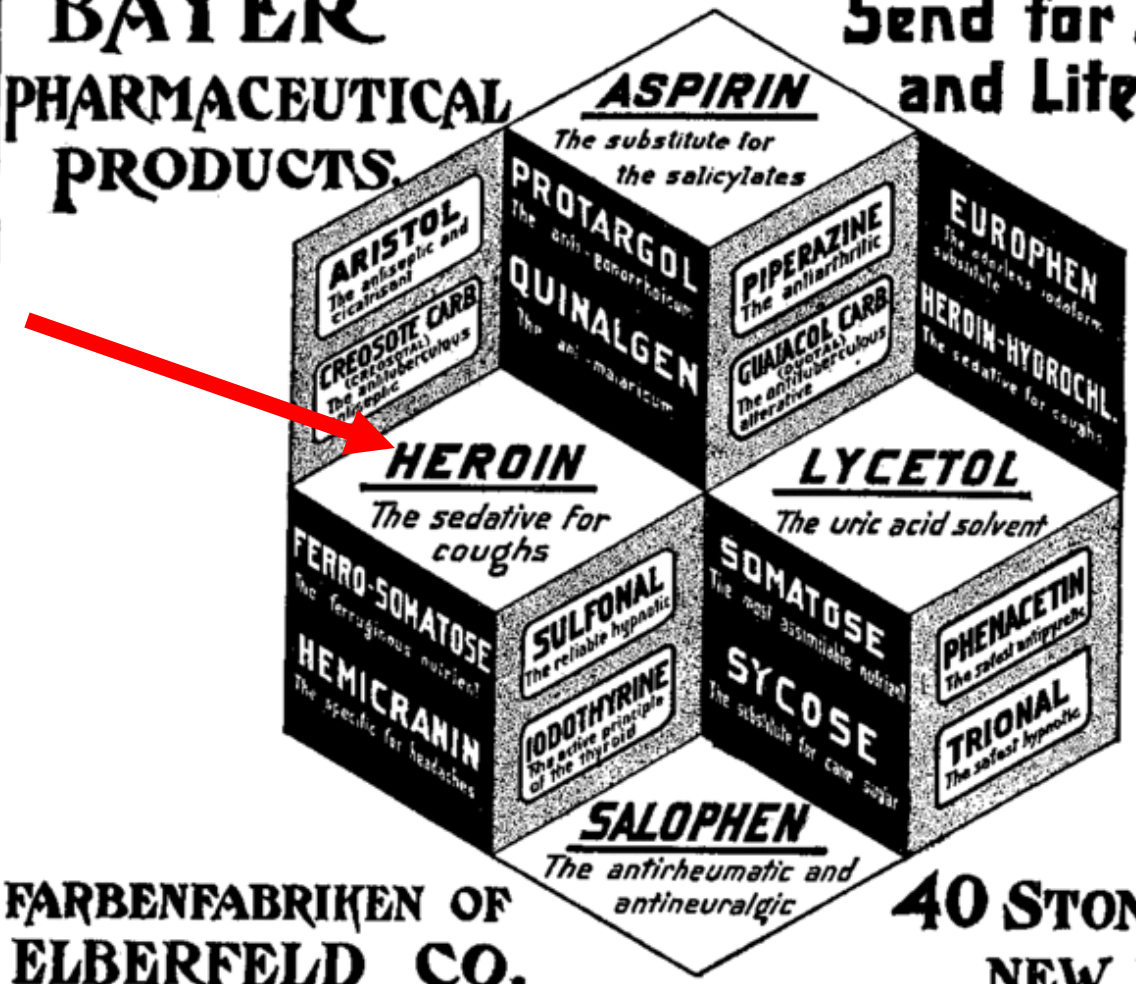
Objectives

- Learn basic addiction neuropathology
- Learn SUD criteria, Definition of *Addiction*
- Recognize individuals who should be referred for SUD evaluation
- Learn the benefits of MOUD
- Demonstrate data that OBOT is safe and effective in Primary Care

BAYER
PHARMACEUTICAL PRODUCTS.

Send for samples and Literature to



FARBENFABRIKEN OF ELBERFELD CO.

40 STONE STREET, NEW YORK.

Why can't people just stop?

- Addiction is a Chronic Brain Disease
- With Opioid Use Abuse, changes in brain can persist for longer than 3 years--This is not true of cocaine
- Data is Clear and Overwhelming, Evidence base supports primary treatment with medication treatment

Lifetime Prevalence of SUD

- 12-15% of Americans
- 30% of children of alcoholics
- 28-33% of people on chronic opioids

NIDA; Boscarino JA et al. J Addictive Dis 2011; 30:185-194

What is Drug Addiction?

- Addiction is a chronic relapsing brain disease
- Characterized by compulsive drug seeking and use, despite harmful consequences
- Drugs of abuse change the structure and function of the brain
- These brain changes can be long-lasting, and can lead to harmful behaviors

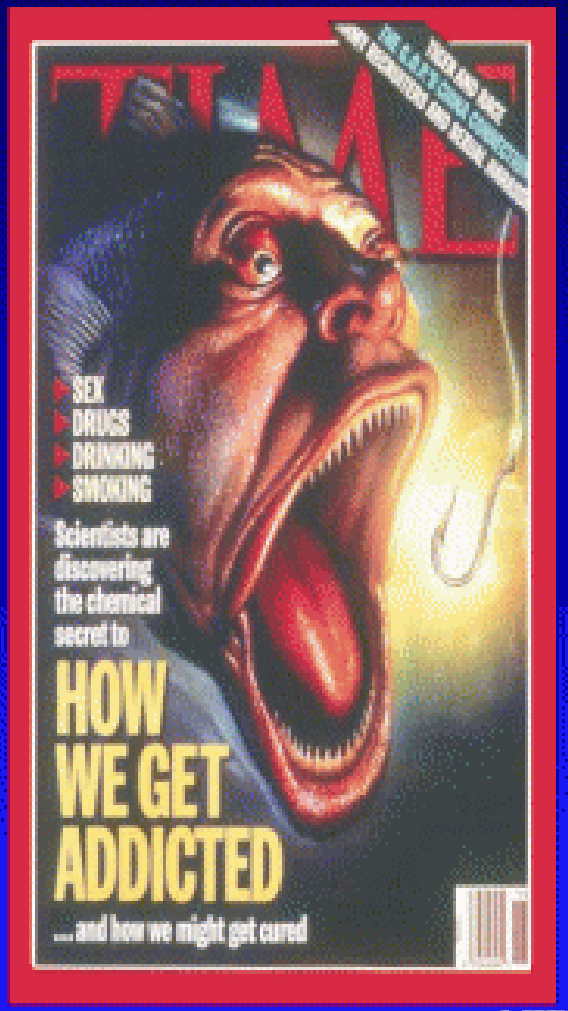
Addiction

Neurobehavioral condition with genetic and environmental factors

- Chronic
- Craving
- Compulsive
- Continues despite real/potential harm

Why Do People Abuse Drugs?

Drugs of Abuse Engage *Motivation* and *Pleasure Pathways of the Brain*



NIDA

Substance Use Disorder DSM V?

- Problematic, Maladaptive **pattern**
- Leading to clinically significant impairment or distress
- Including at least 2 of the following and occurring within 12 months:

1. ***Tolerance*** *2.* ***Withdrawal*** *signs* **not** a criteria when on Rx opioids

3. Substance taken in larger amounts/longer period of time than intended

4. Unsuccessful efforts to quit/cut back

5. Energy, time and effort to obtain, use or recover from substance

6. Strong desire/craving for substance

Motivational Injury

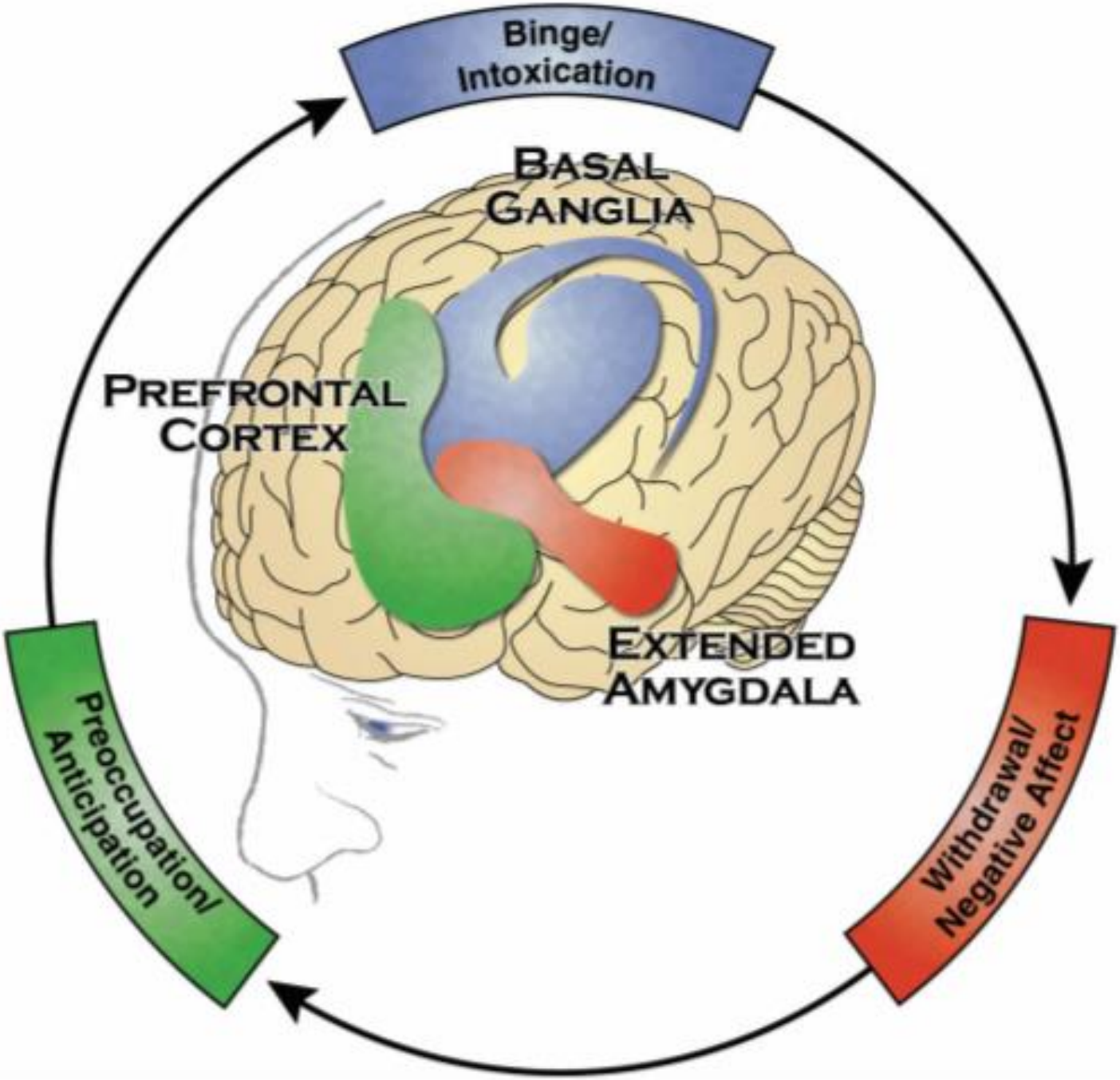
7. Use interferes with major role obligations: work/school/home

8. Continues despite impact on social and interpersonal relationships

9. Used in situations where it may be physically hazardous

10. Social, occupational, recreational activities reduced eliminated

11. Use despite knowledge of medical or psych. problem resulting from use


Binge/
Intoxication
Basal
Ganglia
Prefrontal
Cortex
Extended
Amygdala
Withdrawal/
Negative Affect
Preoccupation/
Anticipation

Three Stage Cycle of OUD Neuropathological Correlates

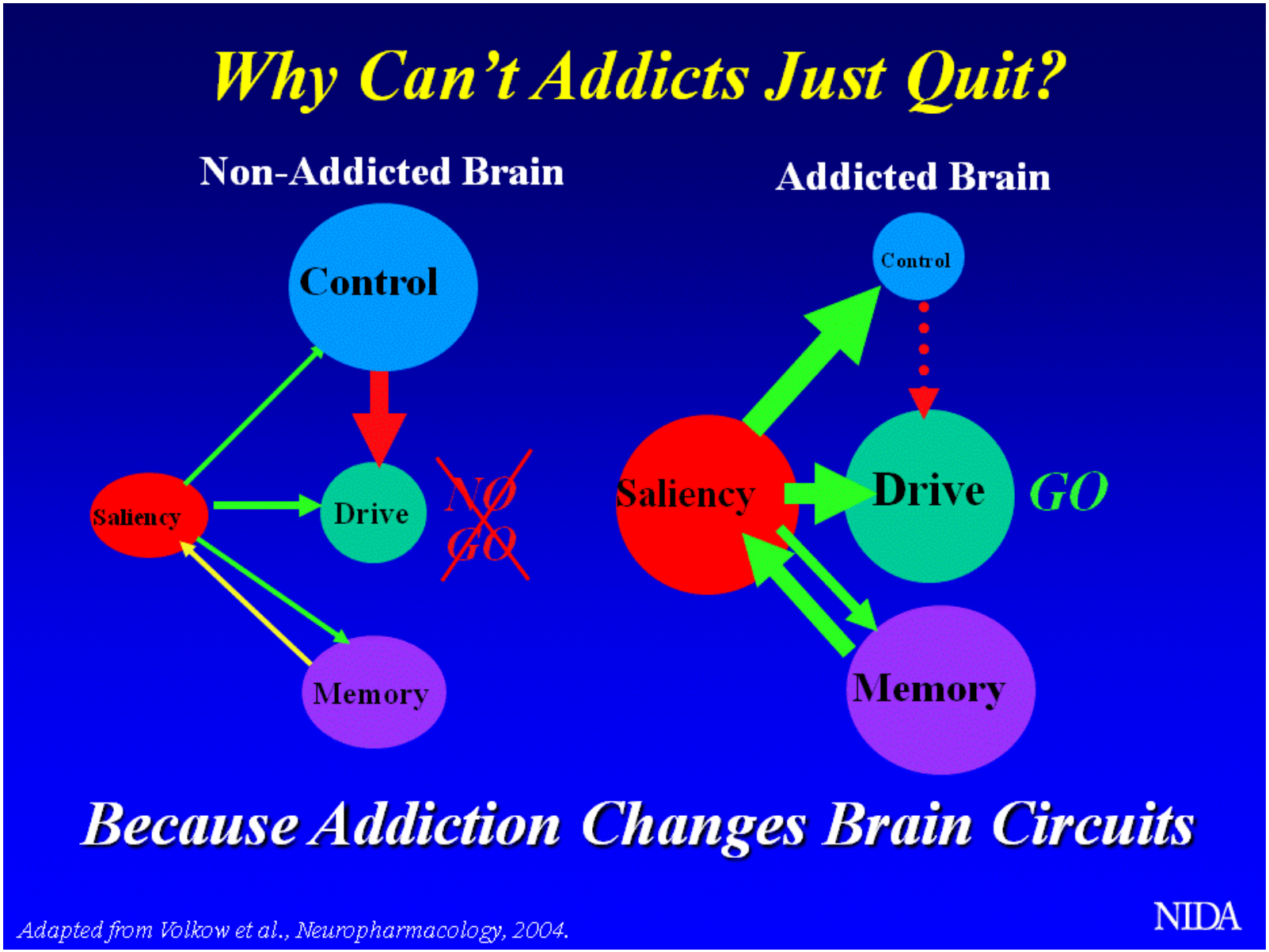
- Each results in drug-induced changes in multiple brain circuits

1. **Binge/Intoxication** involves opioid-induced reward sensations in brain
2. **Withdrawal/Negative** affect characterized by elevation in the threshold for experiencing the reward sensation after drug use (ie, increased exposure to the drug is required) and a withdrawal state develops when the drug cannot be obtained
3. **Preoccupation/Relapse** is characterized by chronic relapse in drug use, often triggered by environmental and emotional cues. Chronic opioid use induces neurochemical changes that alter brain circuits. This reduces the reward sensation experienced during the initial stage and increases the stress and compulsivity associated with chronic drug addiction

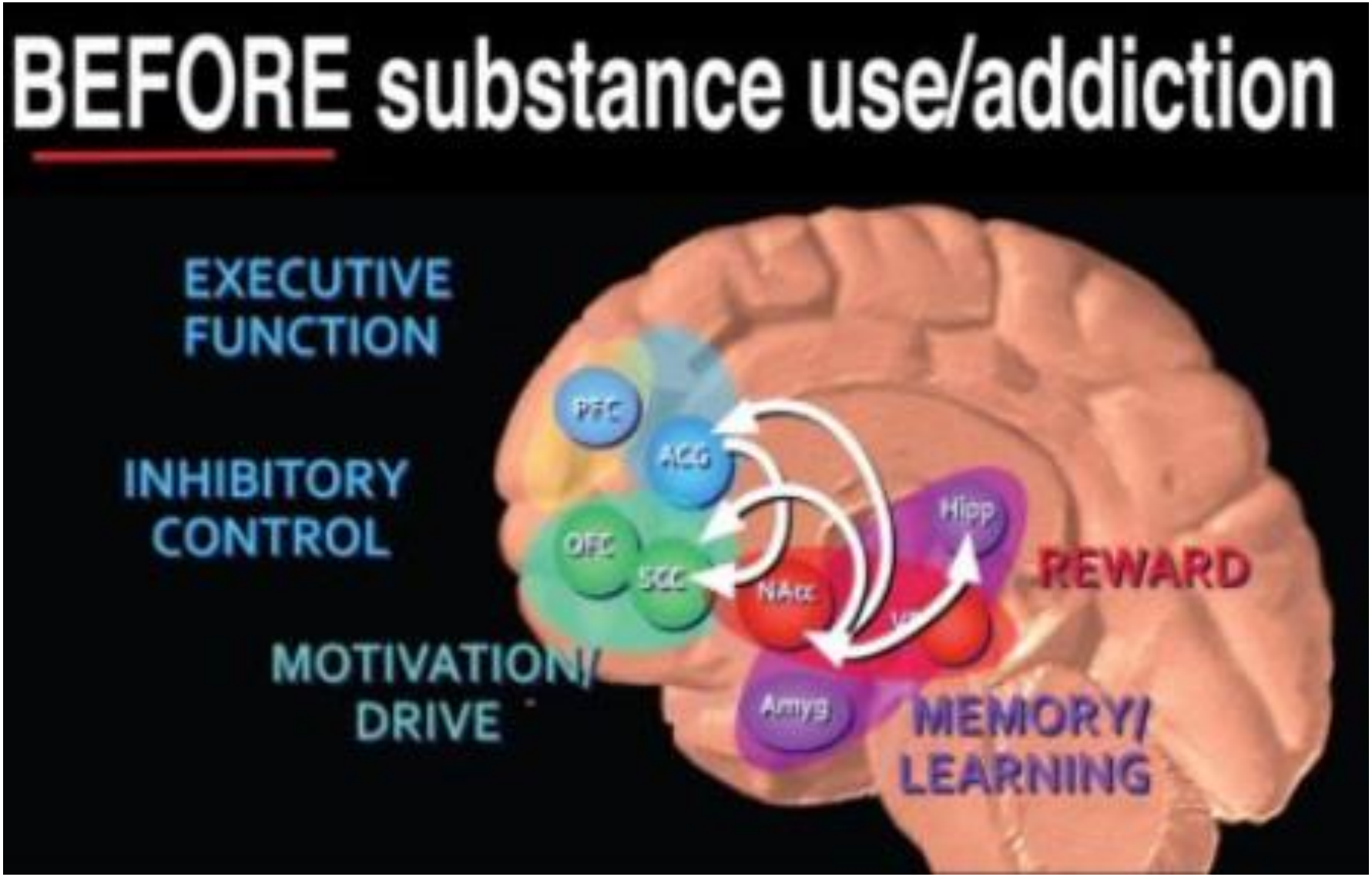
JAMA. online April 26, 2018. doi:10.1001/jama.2018.3394

Neuroplasticity and Addiction

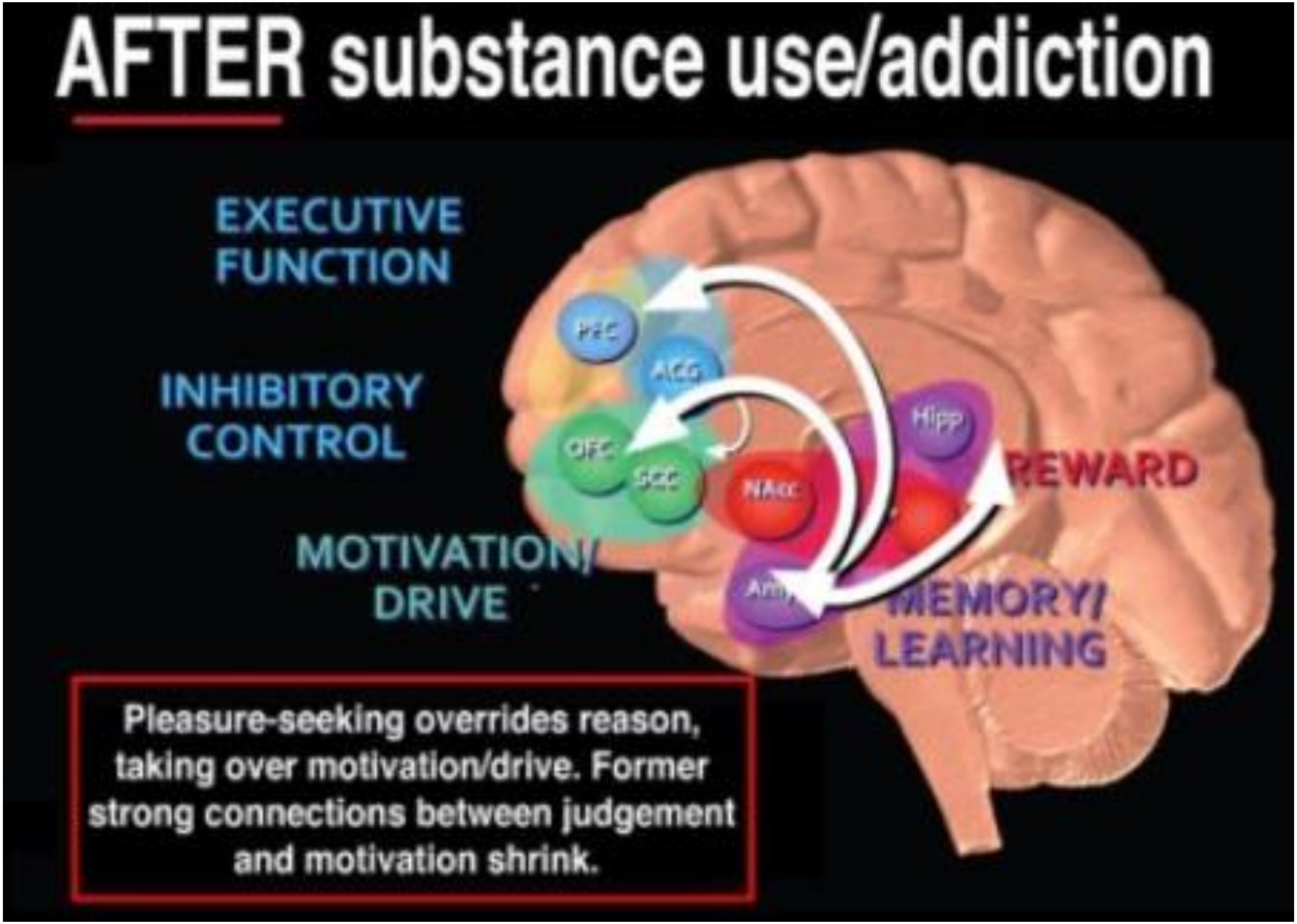
- Re-enforcing / addictive substance use
- Mimic physiologic DA firing but it is more intense and more protracted
- This results in a supraphysiologic salient stimuli
- HIGHLY salient = driving attention, arousal, conditioned learning and motivation
- Repeated doses raise the thresholds required for DA cell activation and signaling
- Drug abusers have marked decreases in D2 receptors and D2 release



Addiction and Changed Brain Circuits

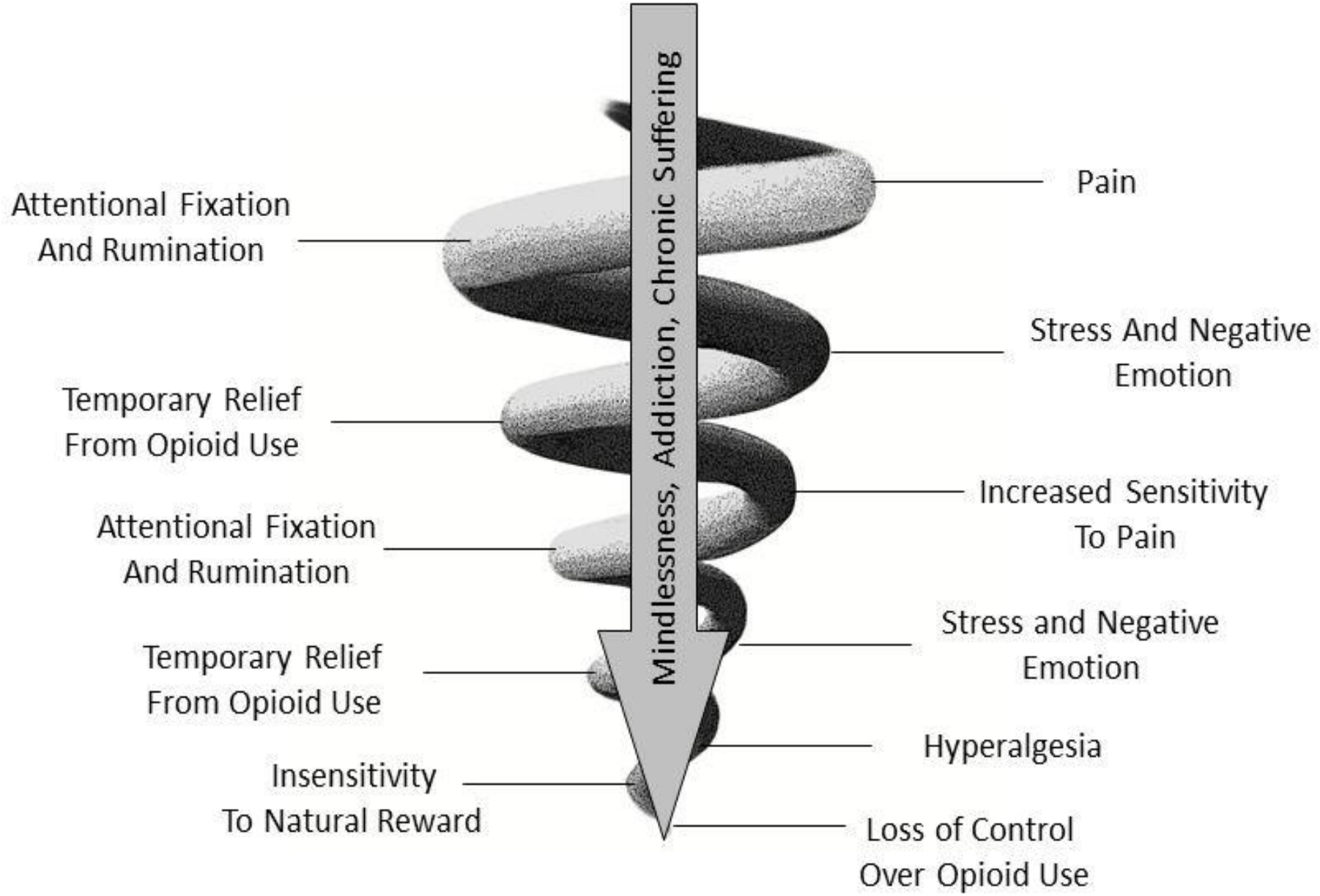

BEFORE substance use/addiction
EXECUTIVE FUNCTION
INHIBITORY CONTROL
MOTIVATION/ DRIVE
REWARD
MEMORY/ LEARNING
PFC
ACG
OFC
SCC
NAcc
Hipp
Amyg

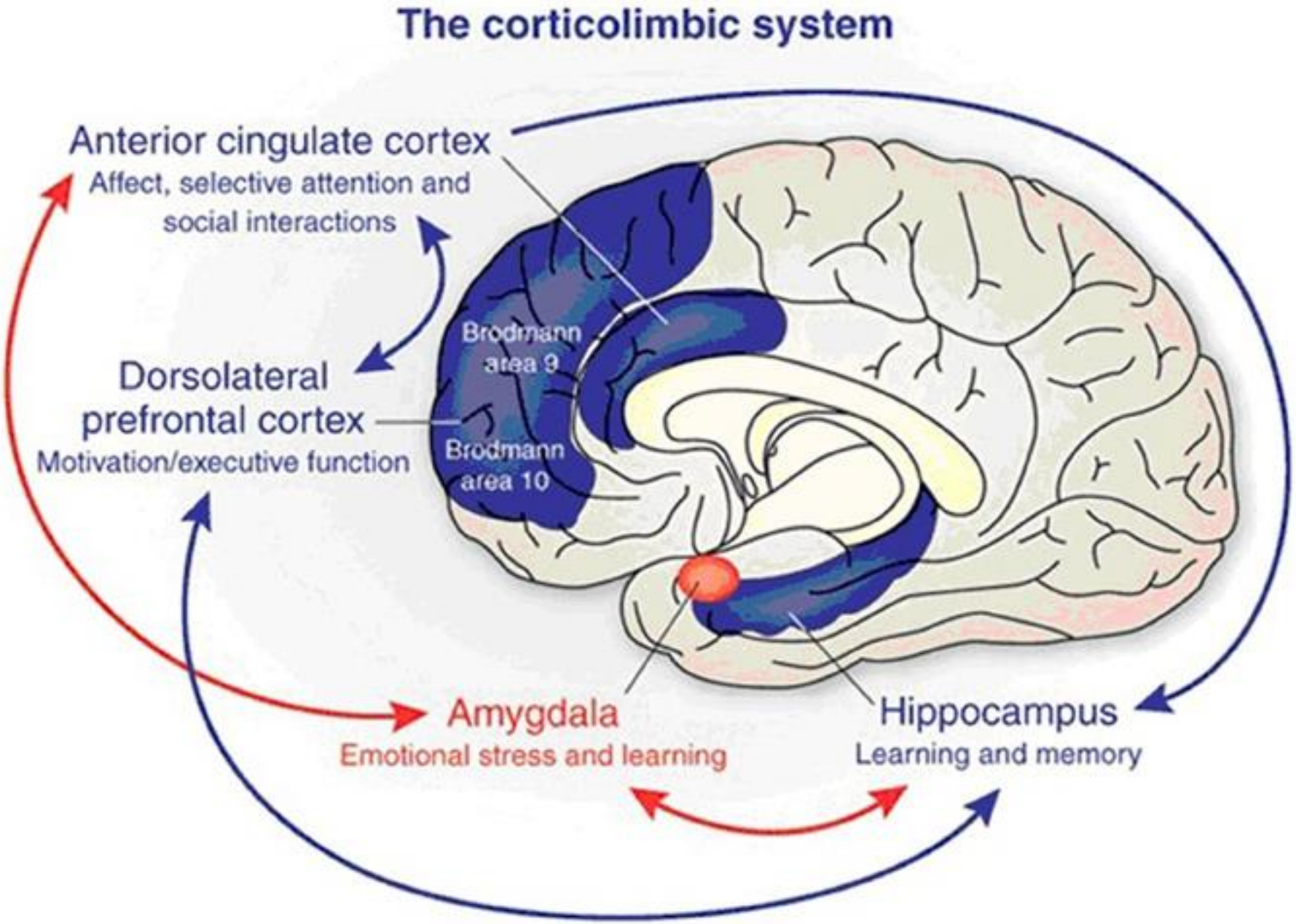
AFTER substance use/addiction



Plasticity: Hard Wired Addiction

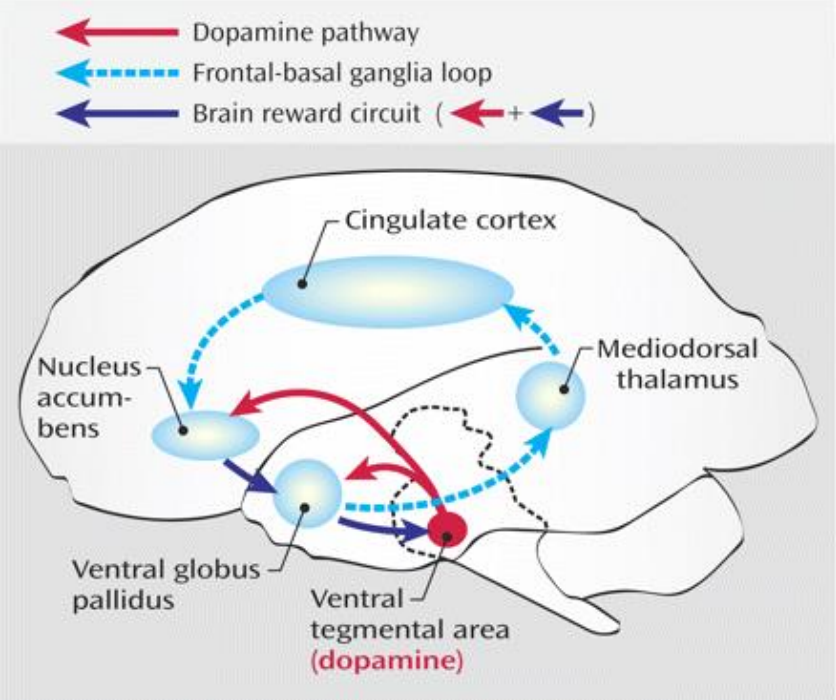
- Conditioning triggered by drug causes enhanced DA signaling when one experiences conditioned cues (seeking cues)
- This drives motivation to seek out and procure
- Activation of PFC and striatal regions
- Therefore, regional deficits induced by drug use link PFC/striatal to loss of control and compulsive drug intake when he/she is exposed to and or takes drug
- <u>These deficits reduce ones' sensitivity to natural reinforcers</u> (harder to find pleasure/satisfaction)


Mindlessness, Addiction, Chronic Suffering
Attentional Fixation And Rumination
Pain
Stress And Negative Emotion
Temporary Relief From Opioid Use
Increased Sensitivity To Pain
Attentional Fixation And Rumination
Stress and Negative Emotion
Temporary Relief From Opioid Use
Hyperalgesia
Insensitivity To Natural Reward
Loss of Control Over Opioid Use



Addiction is a Chronic disease of the Brain

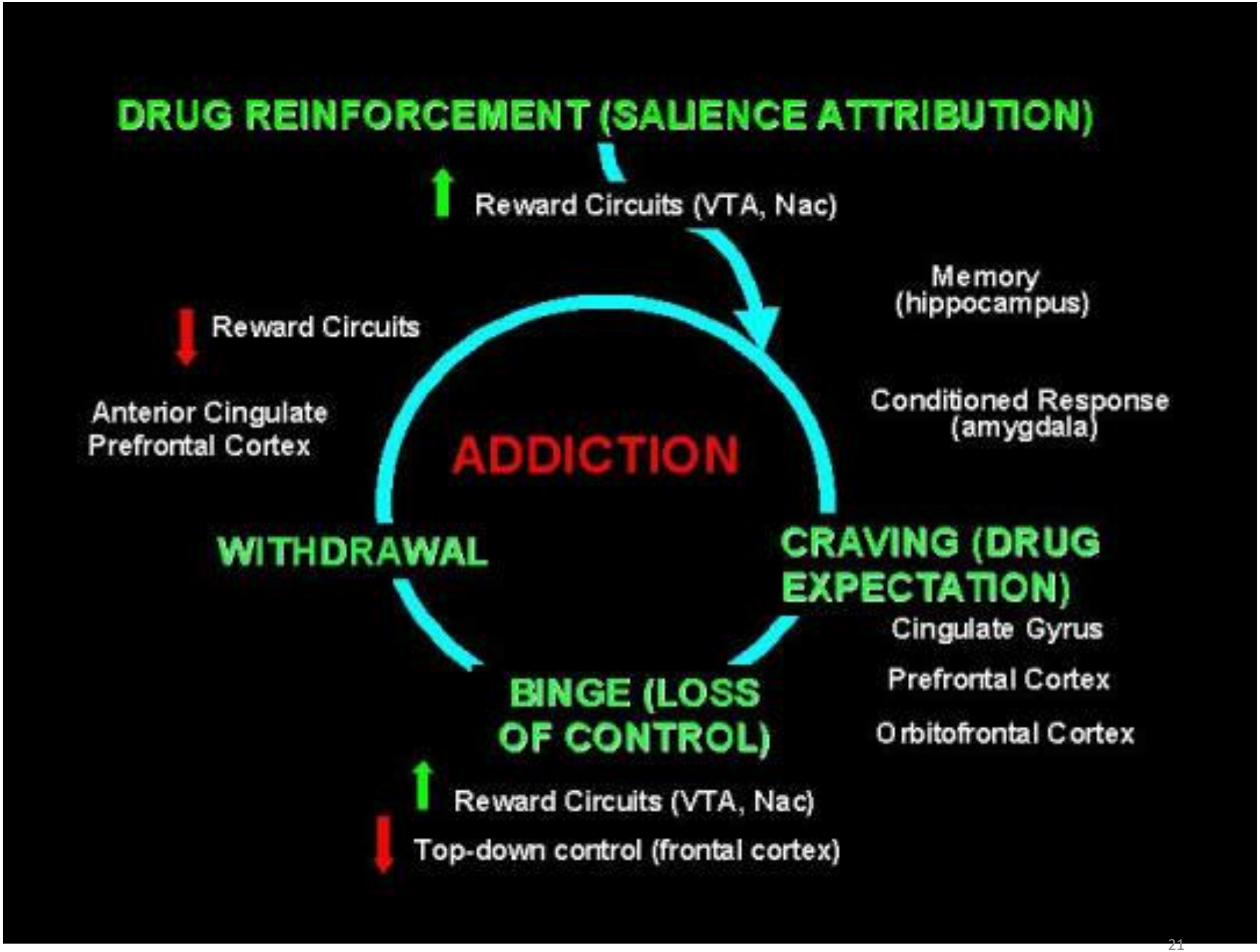
Not a failure of morals or character



- **Environment**
- **Genetic**
- **Mental illness**
- **Youth to 25**

➢ **Neuroplastic**

➢ **Chronic**


DRUG REINFORCEMENT (SALIENCE ATTRIBUTION)
Reward Circuits (VTA, Nac)
Memory
(hippocampus)
Conditioned Response
(amygdala)
CRAVING (DRUG
EXPECTATION)
Cingulate Gyrus
Prefrontal Cortex
Orbitofrontal Cortex
BINGE (LOSS
OF CONTROL)
Reward Circuits (VTA, Nac)
Top-down control (frontal cortex)
WITHDRAWAL
Reward Circuits
Anterior Cingulate
Prefrontal Cortex
ADDICTION

Mr. William Sobert

- 56 Chronic LBP pain >10 yrs.
- **COT for ~ 5.8 yrs.**
- Knee
  - Mild-moderate tricompartment
- Facet degeneration, DDD
- L4-5 fusion in **2015**
- Hydroc. 10/325 each 6-8 hr “prn”
- Tramadol 3/day Miralax, PPI, CPAP, paroxetine, “T”
- Temazepam 15 mg/ night “prn”

William B. Sobert

- Care-giver to mother, 83
- Disability 2016**
  - Half-Price Books
- 3 early RFs in 12 months
- 2017 UDM **on Day 24/28**
  - No tramadol / norhydrocodone
- FHx –Etoh, opioids, cocaine
- Cocaine + 1995
- Etoh- 230, 198, 347 (1990-1996)
- Divorced 1999
- Altered Mental Status in ED 2017
- 2018 “fired” UDM ++ **morphine**

Willie B. Sobert

Now What?

We are what we think. All that we are arises with our thoughts. With our thoughts, we make the world

9 days after her OD

Good Morning. Sue Here. I didn't use over the weekend but wanted to check in with you and let you know that I have pretty bad cravings, horrible night sweats and Everything is a trigger.

To give you an example, I was watching Madagascar with my grandson. The animals lost all the water in the reserve. The lion, Alex, and his dad restored the water.

The thirsty hippos and giraffes and water buffalo were standing there watching the water come with expressions of absolute joy, glee, anticipation of a feeling of salvation and I thought, that's what heroin feels like.

NSDUH (SAMSHA) Data 2015

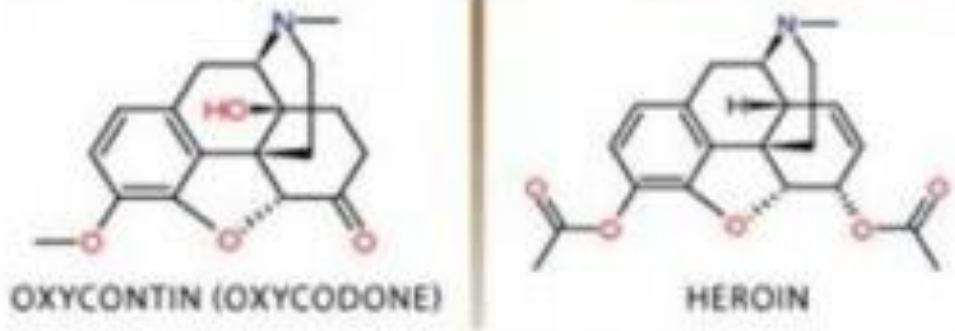
- Survey results indicated that 38% of U.S. population used an opioid in 2015 (approx. 91.8 million people)
- Among Adults with opioid Rx
  - 12.5% reported misuse
  - Among 12.5%, 16.7% indicated they had a OUD
- Of all adults who reported misusing opioids
  - 40% with a Rx, and **60% without an Rx**
  - Among the 60%, 41% obtained opioids illicitly for free from friends and family
- Among adults who misused opioids 63% reported **relief of pain as motivation**

Ann Intern Med. 2017;167(5):293-301

Population-based, observational study using data from many sources

- Substance abuse indicators decedents 94%
- Prevalence of diversion decedents 18-24%
- Opioid analgesics used decedents 93%
- Multiple substances implicated 79%
- Had Past Med history of SUD 78%
- Rx from 5 or more clinicians in the year prior to death was more common among women

JAMA. 2008;300(22):2613-2620


HO
OXYCONTIN (OXYCODONE)
HEROIN

Low Hanging Fruit?

- prevalence of opioid abuse in chronic pain patients ranges between **20-24%** across health-care settings.
  - Pain 2010, 150(2):332–339

- Lifetime prevalence of DSM-V OUD those on chronic opioids
  - **9.7 %** moderate & **3.5 %** severe OUD
  - Substance Abuse and Rehabilitation 2015:6 83–91

10-18% - my opinion for prevalence in those on opioids for chronic pain

Risk of SUD/Abuse

OR (adjusted) when exposed to:

122	**≥120 MED/day**
29	**36-120 MED/day**
15	**1-36 MED/day**
1	**no opioid Rx** (considered non-exposed)

Note: The risk of abusing drugs and developing a SUD dramatically increases with increasing morphine equivalent dose (MED) per day

Clin J Pain 2014; 30(7):557-564

Condition	Prevalence Chronic Pain Patients
Depression	33% - 54%[22,23]
Anxiety Disorders	16.5% - 50%[22,24]
Personality Disorders	31% - 81%[25,26]
PTSD	49% veterans[27]; 2% civilians[24]
Substance Use Disorders	15% - 28%[22,25]

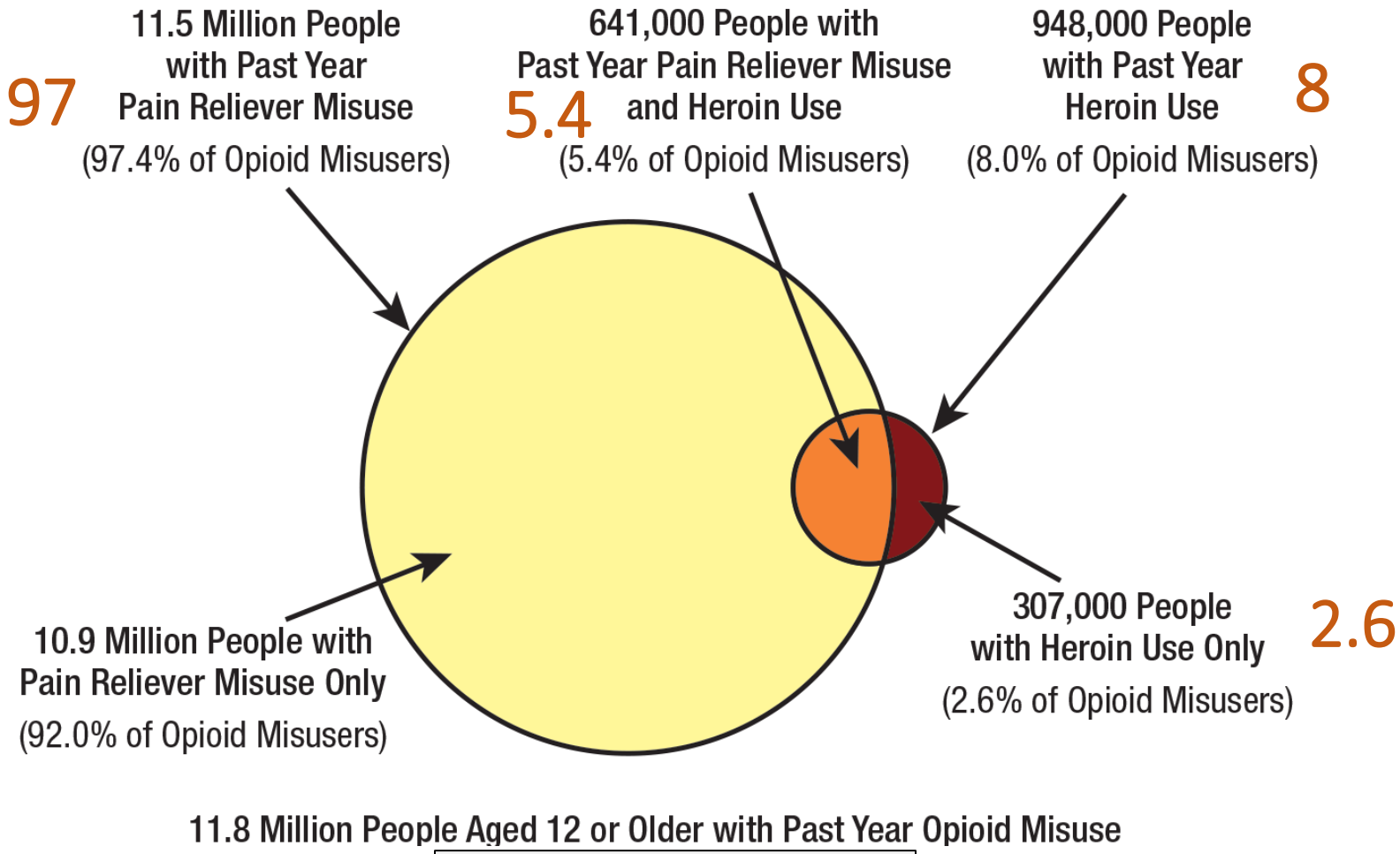
PTSD, posttraumatic stress disorder.

Gen Hosp Psychiatry. 2012;34(1):46-52
Curr Psychiatry Rep. 2006;8(5):371-376.
J Clin Psychol Med Settings. 2011;18:145-154
SCOPE of Pain, Boston Universtiy

16% with mental illness get 51% of opioids

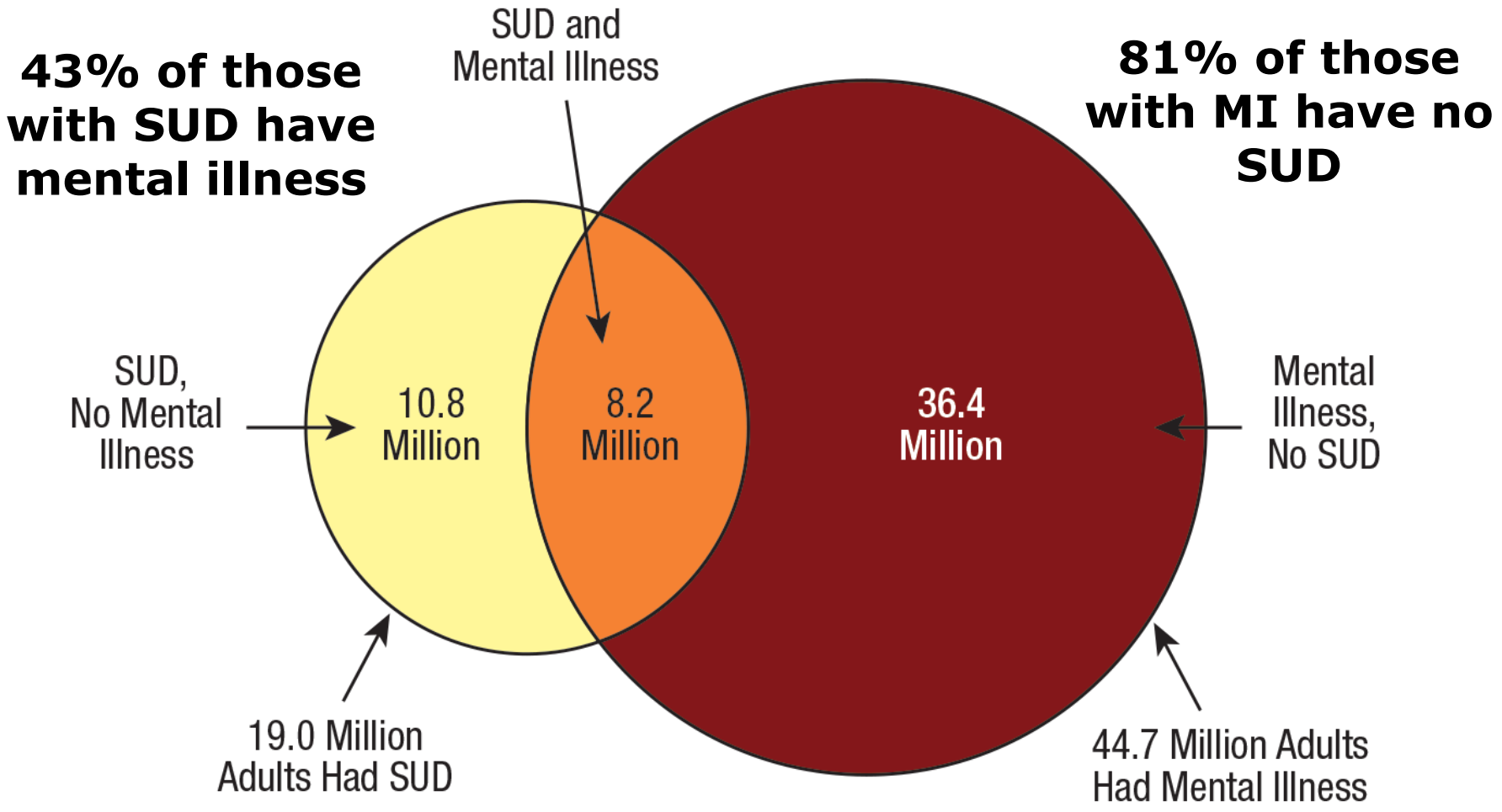
J Am Board Fam Med 2017;30:407– 417

Overlap of Pain Reliever Use and Heroin Use



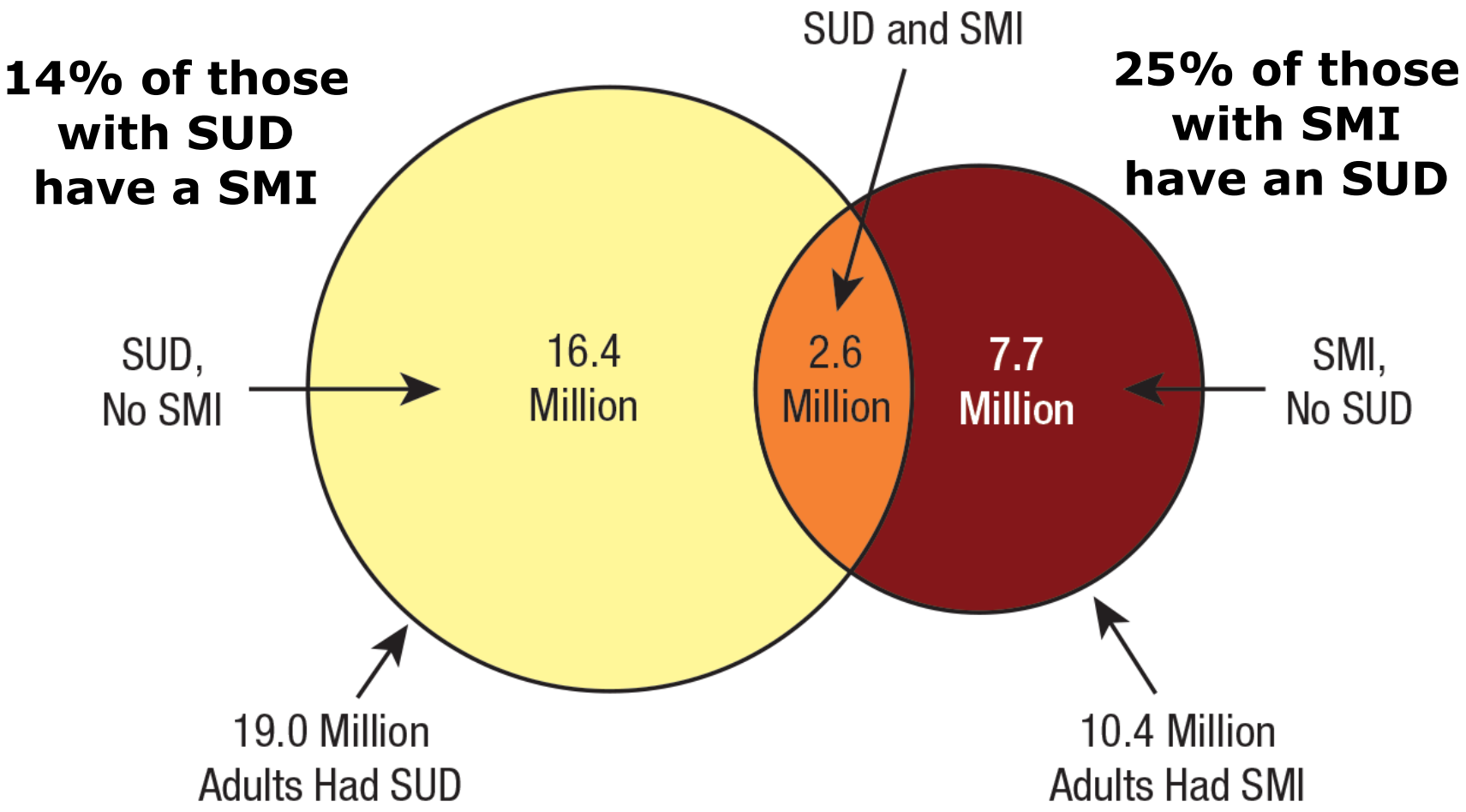
NSDUH 2016

Overlap of Mental Illness and SUD



2016 NSDUH

Overlap of SERIOUS Mental Illness (SMI) and SUD



2016 NSDUH

Access to MATs Saves Lives

A study of heroin-overdose deaths in Baltimore between 1995 and 2009 found an association between the increasing availability of methadone and buprenorphine

50% decrease fatal overdoses

Am J Public Health 2013;103:917-22

MOUD:
Medication for Opioid Use Disorder

- Methadone
  - **Agonist** – controlled management of addiction
  - Federal clinics regulated by DMHA
  - 13 programs in Indiana
  - Can be used for slow wean or chronic maintenance
  - Daily observed oral dose at clinic
  - Coupled with counseling and support services
  - Well-studied and effective
  - **Cash pay and Medicaid covered for MAT in Indiana**

MOUD

- Buprenorphine – OUD formulations
  (*Subutex/Suboxone/Zubsolv/Belbuca/Bunavail*)
  - **Partial agonist mu** and delta & ***k*** antagonist
  - Shown activity at the opioid receptor like receptor (ORL-1), which has been shown to offset some actions of morphine, namely the antinociceptive and reward action
  - *Some have an* antagonist, naloxone
  - Decreased risk of overdose/abuse
  - Office-based treatment, 24 hr. abstinence
  - Sublingual dosing and new injection/depot formulations
  - Physicians DEA training/certification
  - Limitations on number of people an individual provider can treat
  - Covered by Medicaid

MOUD

- Naltrexone
  - **Antagonist** – blocks all effects of opioids
  - Obesity, AUD, OUD, Tobacco, ADF & FM Tx
  - Oral and injectable forms (long-lived)
  - **Must be totally detoxed prior to use, > 7 days**
  - Effective for opioid and alcohol addiction treatment
  - Can “override” blockade with high doses of opioids
  - Hepatotoxicity, injection reactions
  - Works best in highly motivated individuals – parole, probation, early release, **not after OD**

Science Matters More Than Opinion

- United States x-Secretary of Health and Human Services Tom Price, praised Vivitrol while in Ohio
- Price had claimed that buprenorphine and methadone were "simply substitute[s]" for "illicit drugs"
- Almost 700 experts in the field of substance abuse submitted a letter to Price cautioning him about Vivitrol's "marketing tactics" and warning him that his comment "ignore widely accepted science".
- Buprenorphine and methadone, are "less expensive", "more widely used", and have been "rigorously studied“
- See New York Times article, June 2017

Integrative Addiction Care and Methadone

- 2005 Study with full complement of behavioral, psychological, medical and social support systems
- $38 benefit for each $ 1.0 spent on programs
  1. Less healthcare utilization
  2. Reduced spread of infectious illnesses
  3. Fewer overdoses
  4. Better employment
  5. Reduction in crime

What Good Will Come

Outcomes	No MOUD	Methadone
Retention	154/1000	**684/1000**
Morphine +urine	701/1000	**463/1000**
Criminal Activity	118/1000	**46/1000**
Mortality	17/1000	**8/1000**

Medication for Opioid Use Disorder After Nonfatal Opioid OD and Association With Mortality

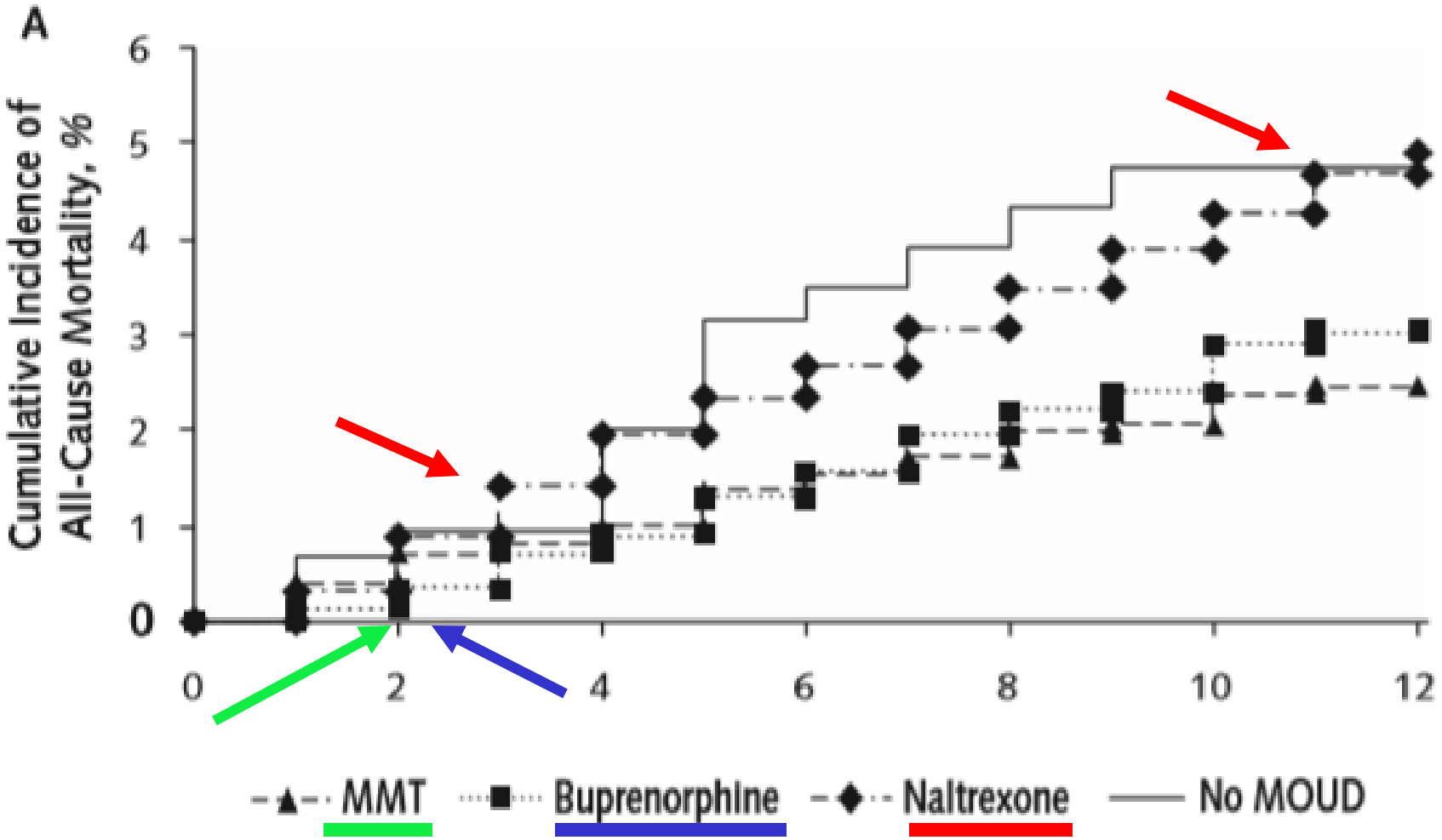
- 17568 Massachusetts adults without cancer who survived an opioid overdose between 2012 and 2014
- Over the 12 months after nonfatal OD :
  - Methadone 11% for median 5 mo
  - Buprenorphine 17% for median 4 mo
  - Naltrexone 6 % for median 1 mo
- Multivariable Cox proportional hazards model
  - All cause mortality and opioid related mortality
  - Fewer than a third of participants received MOUD in the 12months after nonfatal opioid overdose

Ann Intern Med 19 June 2018

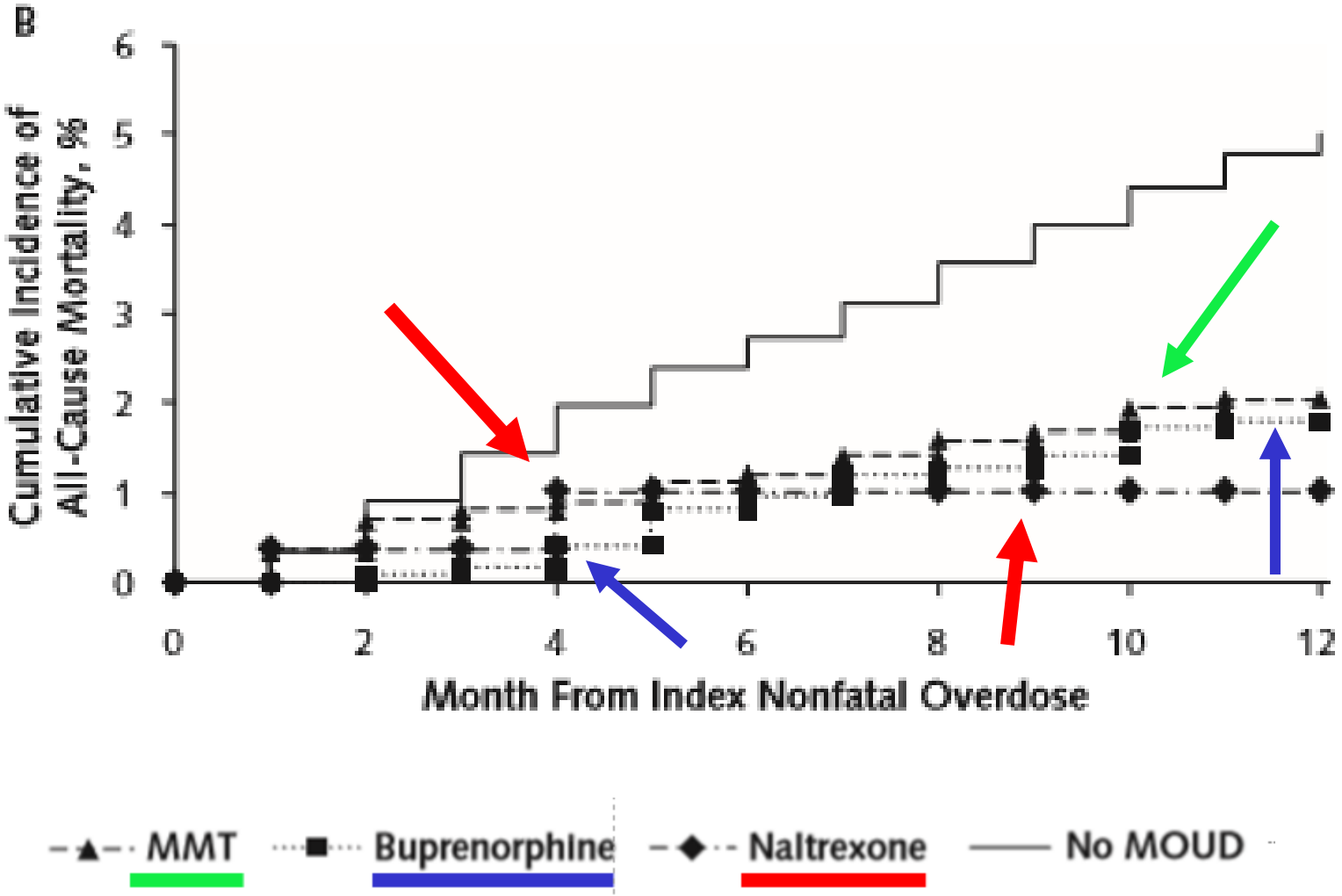
Care After Nonfatal OD and Mortality

	No MOUD	MMT	BUP	NTX
Exposure, person-months	172791	13324	17955	3310
All Cause Mortality				
Deaths	724	27	46	14
Adj. Hazard Ratio	1.0	0.47	0.63	1.44
Opioid Related Mortality				
Deaths	**	15	30	**
Adj. Hazard Ratio	1.0	0.41	0.62	1.43

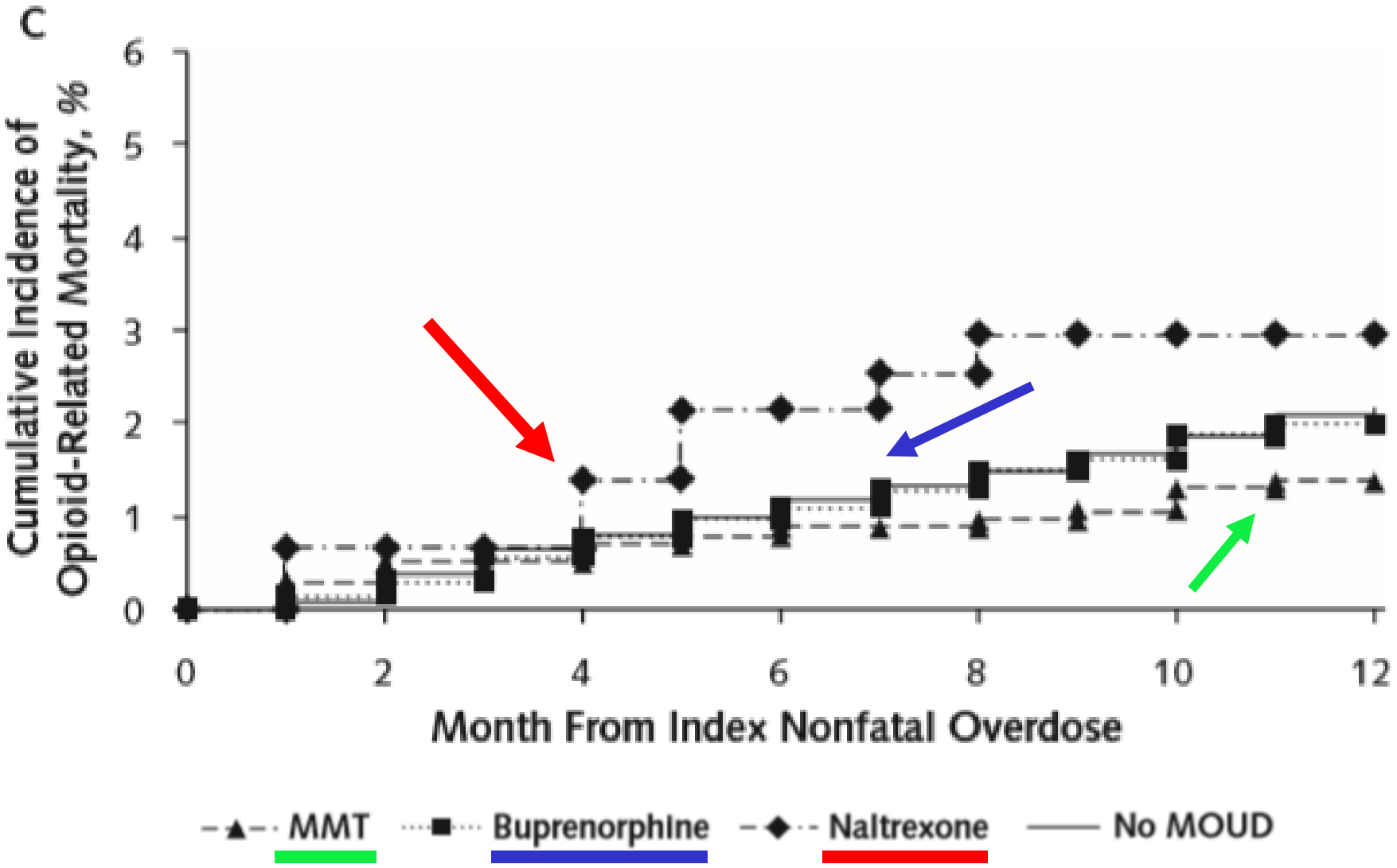
OUD Treatments and all cause mortality after nonfatal OD



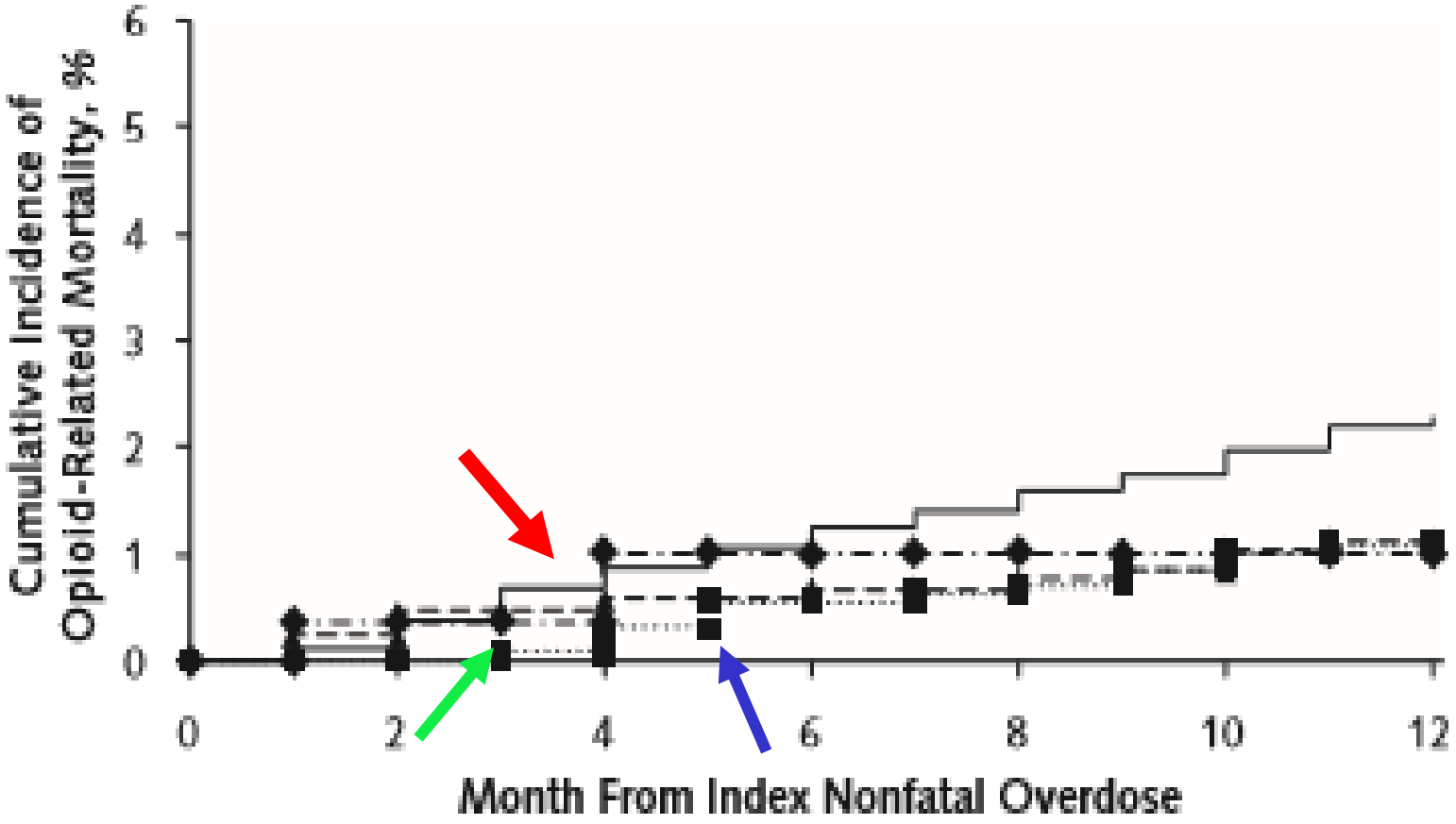
Secondary Exposure Classification: On Treatmentt



Opioid Related Death after Nonfatal OD
Primary Exposure



Secondary Exposure Classification: On Treatmentt



Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial

- 24-week randomized and open-label
- Buprenorphine/naloxone vs. NTX-XR (intramuscular)
- primary outcome was opioid relapse-free survival during 24 weeks of outpatient treatment. Relapse was 4 consecutive weeks of any non-study opioid use by urine tox. or self-report, or 7 day in row of self-reported use.
- successfully initiated: NTX-XR **72%** and BUP-NX **94%**
- NTX-XR participants reported less craving early in study
- Relapse NTX-XR > BUP-X (**65%** vs **57%** HR of 1.36)
- Most were early relapses with NTX-XR

Lancet 2018; 391: 309–18

Telemedicine and OUD Treatment

- OBOT with bup. in rural Maryland, N=300
  - 59% remained in Tx after 3 mo. and
  - 94% of those were free of illicits (1)
- W. Virginia pilot of 2 years: face2face = telemedicine
  - Additional substance use
  - Ave. time to get 30 and 90 days of consecutive abstinence
  - Treatment retention @ 90 & 365 days (2)
- Can be done in Indiana, need to collaborate
- Can help confidence and transition to MAT provider

1. **Welsh et al 49th Annual Conference of the American Society of Addiction Medicine**
2. **J Addict Med 2017;1(2):138-144**

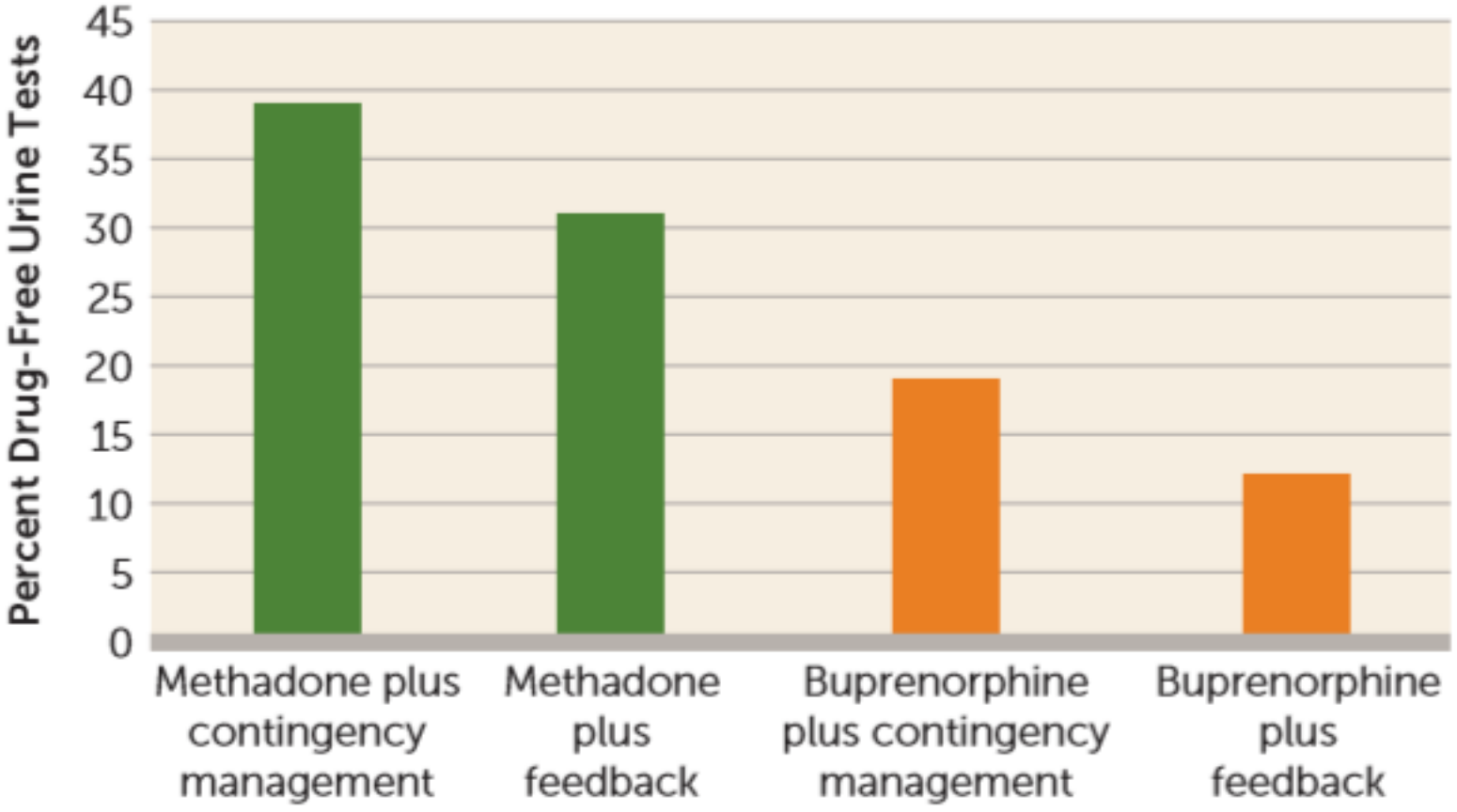
Is significant behavioral support always needed when using buprenorphine

- Clearly 20-25% of those with serious mental illness would benefit with psych. support beyond that offered by waivered providers
  - Dual-diagnosis best care for these people
- Those with active polySUD could benefit with robust treatment
- Those with interest in or a perceived need for psych. care may benefit
- Number of studies show that specialty psych. care with OBOT adds little to outcomes

Some data

- Four key RCTs showed no benefit in adding a behavioral intervention to buprenorphine plus medical management, and four studies indicated some benefit for specific behavioral interventions, primarily contingency management.
  - AmJPsychiatry2017;174:738–747
  - Addiction 2013 Oct; 108(10):1788–1798
  - Arch Gen Psychiatry 2011 Dec; 68(12):1238–1246.
- Just call it Treatment
  - Addict Sci Clin Pract 2012 Jun 9; 7(1):10
- We need more access to care and OBOT is very helpful and far safer than no care
- Step-Care model with frequent visits and in conjunction with community resources/PEERS

Outcomes by Treatment Condition in a 2005 Study of 162 Cocaine- and Opioid-Dependent Individuals Who Received Either Methadone or Buprenorphine Plus Either Contingency Management or Performance Feedback[a]



Meta-analysis of MOUD

- 370,611 participants (1,378,815 person-years)

	pooled all-cause CMRs
While receiving MAT	0.92/ 100 person-years
After MAT cessation	1.69
Untreated period	4.89
MM-Bup. (during/post)	0.93 // 1.79
NTX (during/post)	0.26 // 1.97
	pooled OD CMRs
While receiving MAT	0.24
After MAT Cessation	0.64
Untreated period	2.43

Molecular Psychiatry:22 June 2018

Summary: Reasons for Optimism

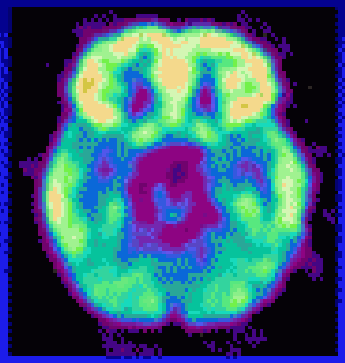
- Science-based compassionate communication
- Medicalize SUD- Look for Patterns
  - Better screening and Metric use
  - Questions: History and Genetics predict
  - MOUD- three options that keep people in treatment
  - Bup. And Methadone with greater evidence
  - Buprenorphine and MMT were associated with reductions in all-cause and opioid-related
- OBOT- very effective for most with OUD
  - W or w/o significant psych. support
- Warmly direct to addiction services

- Keep friends close & friends with SUD closer

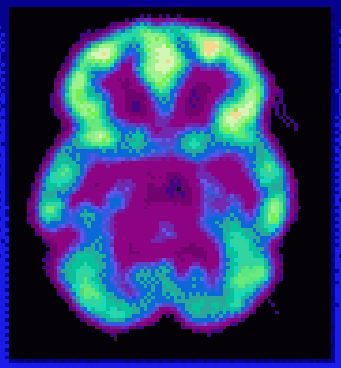
Addiction is Like Other Diseases…

- It is preventable
- It is treatable
- It changes biology
- If untreated, it can last a lifetime

Decreased Brain Metabolism in *Drug Abuser*

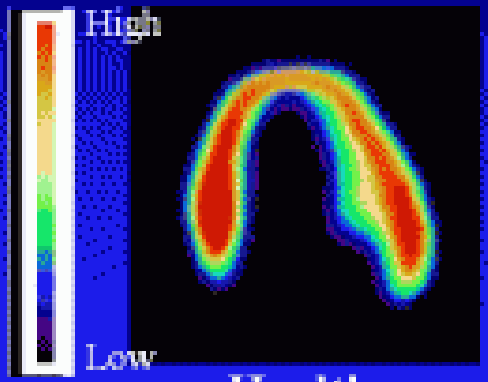


Healthy Brain

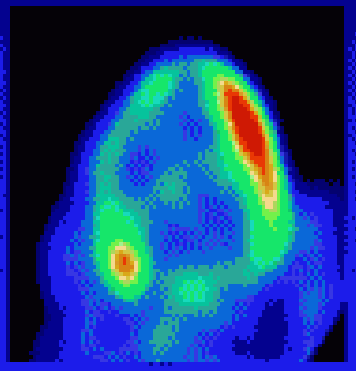


Diseased Brain/ Cocaine Abuser

Decreased Heart Metabolism in *Heart Disease Patient*



Healthy Heart

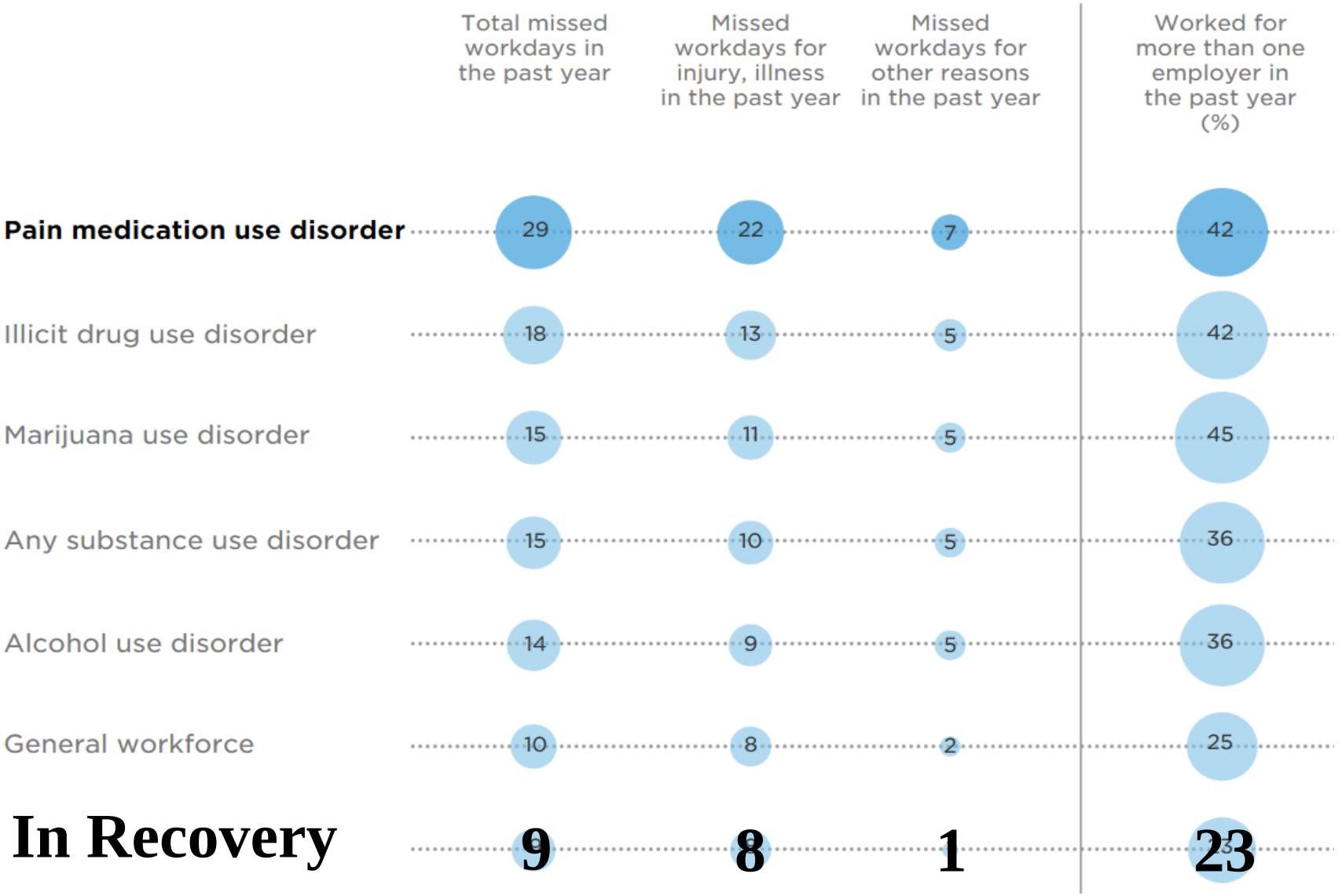


Diseased Heart

Research supported by NIDA addresses all of these components of addiction.

NIDA

The Impact Of Opioid Abuse On Missed Work



Source: *National Safety Council and the NORC research group at the University of Chicago*